Diffusion MRI in Multiple Sclerosis

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Background

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic disease of the CNS that begins most commonly in young adults, and is pathologically characterised by multiple areas of white matter inflammation, demyelination, and gliosis. The clinical course of MS varies from a benign course to a rapidly progressive and disabling disorder. Most patients, however, begin with a relapsing-remitting illness, which is caused by the occurrence of multiple lesions that are disseminated *in time* as well as *in space*. However, after 10-20 years or longer, most patients become disabled. MRI is extremely useful in MS, since it can be used to support the diagnosis of MS and to monitor disease evolution in both natural history studies and treatment trials.

New MRI techniques

Although conventional MRI is the most sensitive paraclinical test in the diagnosis of MS, its specificity is limited. Any pathology from edema and mild demyelination, through to completely necrotic lesions, may show the same abnormal signal. This lack of histopathological specificity accounts, in part, for the modest correlation between clinical disability and MRI parameters, often referred to as the "clinical radiological paradox" [1]. New MRI techniques have been recently developed in order to overcome this limitation, and provide additional *in vivo* information on the pathological substrates of MS. They showed that MS pathology is not restricted to the demyelinating lesions, but also involves the brain outside the lesions, the so-called normal-appearing white matter (NAWM) and grey matter (NAGM), confirming post-mortem data.

Diffusion tensor imaging in MS

Diffusion-weighted imaging is a new MRI technique which has been widely applied in MS to improve our understanding of the disease. In particular, diffusion tensor imaging (DTI) [2], which best describes the diffusion properties of a living tissue, has been employed to investigate the structural damage occurring in the MS brain. From the DT several indices can be derived, such as fractional anisotropy (FA), which quantifies the preferential direction of diffusion within a voxel, and mean diffusivity (MD), which measures the magnitude of water diffusion without regard to its directionality. In the last few years, the growing number of DT studies investigating diffusion abnormalities in MS have consistently reported that diffusion changes are present not only in the demyelinating lesions, but also in the normal-appearing tissue [3-6]. The fact that DTI can detect pathological changes which are not visible on conventional MRI has important clinical relevance because of the potential of pathology in NAWM and NAGM to contribute to disability in patients with MS.

Diffusion-based tractography

Since DTI can detect, at the macroscopic scale of a voxel, the extent of directional bias of diffusion occurring at the microscopic level, it can distinguish between regions where fibres are highly aligned in the voxel from those where fibres are less coherent. However, it provides no explicit information about the connection between adjacent voxels. A number of different tractography methods, which use the information provided by the diffusion tensor concerning the orientation of fibres within a voxel, have

recently been developed in order to determine the pathways of cerebral connections *in vivo* [7]. The possibility of a non-invasive assessment of white matter pathways in MS may increase our understanding of the disease. However, the employment of tractography in MS is still preliminary, and only a few studies have so far examined patients with MS using tractography algorithms [8-11].

This presentation will focus first on methodological aspects, clinical applications and limitations of DTI in MS. Secondly, a few diffusion-based tractography studies will be summarised. Finally, the most common limitations of tractography studies in MS will be discussed.

Methodological aspects

DTI studies in MS have been performed using region of interest and histogram analyses. A voxel-based approach represents a further option (for more details, see [12])

Regions of interest analysis

The majority of DTI papers, especially the less recent, employed this methodology, which consists of drawing regions of interest on specific areas of the brain, using anatomical knowledge, and then quantifying the diffusion parameters, such as FA or MD, within those areas. Regions can be drawn on the non-diffusion weighted b0 images, and then automatically transferred to the DTI maps. Otherwise, they can be outlined on high resolution images, which have to be co-registered to the diffusion maps, and then transferred to the diffusion maps. The main advantages of this approach are that the regions can be chosen on the basis of a priori hypothesis, and can be located on the NAWM ensuring that lesions are avoided, or *vice versa*. On the other hand, using this approach, it is possible to miss significant abnormalities in regions that are not selected. Furthermore, it is highly dependent on the observer and on the anatomical cues used in positioning the regions. The registration process and its related methodological issues must be carefully considered when images from different modalities are co-registered to allow the transfer of regions. It is also necessary to reposition the regions of interest in exactly the same location in longitudinal studies.

Histogram analysis

This approach has been widely used in MS to investigate differences between patients and controls in the NAWM and NAGM and to explore correlations between MRI parameters and clinical disability. The histogram of diffusion parameters is a frequency distribution showing the number of voxels with a particular range of parameter values. From the histogram of each DTI parameter, the following variables can be derived: the mean; the peak height (the proportion of voxels at modal value); the peak location (the location of the modal value). These variables are then used in patients' studies. The histogram analysis allows the characterisation of the diffusion parameters in the whole brain in a fully automated way. Histogram of white matter or grey matter only can also be obtained. In contrast to the region of interest approach, it does not retain any information about location of abnormalities, and avoids any pre-judgment about which parts of the brain is investigated. However, it has been shown that the histogram derived metrics are sensitive to partial volume effect from brain atrophy, and therefore correction for brain volume differences are needed in patients' studies.

Voxel-based analysis

So far this technique has not been applied to MS. It consists of performing an analysis on a voxel-by-voxel basis [13] in order to localise changes related to tissue abnormalities ("VBM-style" analysis). This approach allows us to combine the ability of regions of interest to be spatially specific with the ability of the histograms to be unbiased. In simple terms, it involves co-registration of the diffusion maps, such as FA maps, into a standard space, and then making comparisons of diffusion parameter

values between groups or testing for correlations with an external variable, such as disability or age. Advantages of this approach are that all locations across the brain are tested in an unbiased way, and that location of significant group differences or correlations is automatically shown. Although it presents few problems, such as those related to the registration algorithms and spatial smoothing, it is a powerful technique, and a method that aims to solve these issues has recently been implemented as part of FSL (www.fmrib.ox.ac.uk), and it called Tract-Based Spatial Statistics (TBSS). The application of such method to MS may be further complicated by the presence of MS lesions around the ventricles that, for example, may influence the accuracy of the spatial normalization process.

Clinical applications

Role of DTI in the diagnosis of MS

DTI is not routinely used for the diagnosis or differential diagnosis of MS. Although acute MS lesions have been reported to show increased diffusivity values [14], a reduction of ADC, which is commonly seen in patients with stroke, has also been reported [15].

Role of DTI in assessing the effect of treatments

DTI appears to be sensitive to disease-related changes occurring in MS brain over time [16-18]. Therefore, it has the potential to be used as a treatment outcome measure [3,19]. However, it has not been employed so far in treatment trials mainly because of the lack of standardization of measurements for multi-centre studies. Its ability to detect changes beyond the lesions and its sensitivity to structural damage, combined with the dissemination of high resolution scans and hardware improvements, are encouraging its growing use at multiple clinical sites.

Role of DTI in improving our understanding of the disease

DTI is commonly used in MS to provide insights into the mechanisms of damage in the brain, spinal cord and optic nerve. Here we briefly summarise the main findings:

Brain

1) MS lesions

DTI studies in MS have demonstrated that FA is reduced and MD is increased in MS lesions compared to NAWM and normal brain. Although the highest degree of diffusion abnormalities have been found in T1-hypointense lesions [17,20-23], which are affected by the most severe tissue disruption [24], there is no agreement on the diffusion changes occurring in the enhancing and non-enhancing lesions [20].

2) Normal-appearing white matter (NAWM)

Similar diffusion abnormalities (i.e. reduced FA and increased MD) have been detected in the NAWM of patients with MS compared to the white matter of healthy subjects [21,22,25,26]. Furthermore, diffusion indices in the NAWM have been reported to correlate moderately with clinical disability [23,27-30]. For example, both FA and MD in the cerebral peduncles inversely correlated with EDSS and pyramidal functional score, albeit modestly [27]. Overall, the clinical correlations reported so far suggest that the pathological damage detected on DTI in NAWM regions is a significant factor contributing to disability and progression in MS.

3) Normal-appearing grey matter (NAGM)

Diffusion studies using histogram analysis have described an increased MD in NAGM, including cortical and deep regions, in patients with MS [26,29]. Furthermore, there is evidence that the diffuse damage in the NAGM contributes to clinical disability [29,30]. For example, diffusion histograms

metrics derived from NAGM have been shown to correlate with the severity of language, attention and memory deficits in patients with RR MS [30]. However, conflicting results have been reported on the presence of diffusion abnormalities in the basal ganglia [27,31].

Spinal cord and optic nerve

The spinal cord and the optic nerve have been less studied than the brain, mainly because of technical limitations (i.e. small size, motion artifacts, CSF pulsations). However, encouraging results have been obtained in pilot studies that have applied DTI to the cervical spinal cord in patients with MS [32,33] and diffusion weighted imaging to the optic nerve in patients with optic neuritis [34,35], suggesting that diffusion abnormalities are diffuse to these sites and contribute to the development of irreversible deficits.

Limitations of DTI

The main limitation of DTI studies in MS is that the exact pathological substrates of *in vivo* diffusion changes are not known. Therefore, studies investigating radiological and pathological parameters are needed to understand the underlying tissue abnormalities.

Diffusion-based tractography in MS

Diffusion-based tractography allows us to extend the investigation of diffusion changes from a region of interest of a few voxels to the whole white matter tract [8]. It has also been reported to improve correlations with disability by matching selected tracts with specific clinical scoring systems [10,11]. In a recent study we used tractography to reconstruct the optic radiations of patients with optic neuritis, and found reduced connectivity value in both tracts compared with controls, suggesting mechanisms of trans-synaptic degeneration [9]. Overall, these results show that tractography has the potential to be used not only as a tool to segment white matter tracts and compute FA values, but also to obtain quantitative measures of anatomical connectivity in the most clinically eloquent white matter pathways.

Limitations of tractography

The main limitations of tractography studies in MS are those that are generally found in all tractography studies. For example, they are due to the low resolution of DTI and to the inhomogeneity of white matter structures. These factors determine that DTI cannot adequately reflect the case of a voxel containing more than one population of axonal bundles with different orientations. Moreover, the DTI acquisitions contain noise, and, consequently, the calculated vector direction may deviate from the real fibre orientation. These limitations may induce not only tracking errors [36,37], but also reconstruction of adjacent and unrelated white matter tracts [38]. Furthermore, MS brains contain multiple lesions, and the effect of lesions on tracking is still unclear, although it is possible that, at least some of the tractography algorithms, are able to track through the lesions [9].

References

1. Barkhof F, van Walderveen M (1999) Characterization of tissue damage in multiple sclerosis by nuclear magnetic resonance. Philos Trans R Soc Lond B Biol Sci 354: 1675-1686.
2. Basser PJ, Mattiello J, LeBihan D (1994) Estimation of the effective self-diffusion tensor from the NMR spin echo. J Magn Reson B 103: 247-254.

3. Bakshi R, Minagar A, Jaisani Z, Wolinsky JS (2005) Imaging of multiple sclerosis: role in neurotherapeutics. NeuroRx 2: 277-303.
4. Goldberg-Zimring D, Mewes AU, Maddah M, Warfield SK (2005) Diffusion tensor magnetic resonance imaging in multiple sclerosis. J Neuroimaging 15: 68S-81S.
5. Filippi M, Rocca MA, Comi G (2003) The use of quantitative magnetic-resonance-based techniques to monitor the evolution of multiple sclerosis. Lancet Neurol 2: 337-346.
6. Rovaris M, Gass A, Bammer R, Hickman SJ, Ciccarelli O, Miller DH, Filippi M (2005) Diffusion MRI in multiple sclerosis. Neurology 65: 1526-1532.
7. Mori S, van Zijl PC (2002) Fiber tracking: principles and strategies - a technical review. NMR Biomed 15: 468-480.
8. Pagani E, Filippi M, Rocca MA, Horsfield MA (2005) A method for obtaining tract-specific diffusion tensor MRI measurements in the presence of disease: application to patients with clinically isolated syndromes suggestive of multiple sclerosis. Neuroimage 26: 258-265.
9. Ciccarelli O, Toosy AT, Hickman SJ, Parker GJ, Wheeler-Kingshott CA, Miller DH, Thompson AJ (2005) Optic radiation changes after optic neuritis detected by tractography-based group mapping. Hum Brain Mapp 25: 308-316.
10. Wilson M, Tench CR, Morgan PS, Blumhardt LD (2003) Pyramidal tract mapping by diffusion tensor magnetic resonance imaging in multiple sclerosis: improving correlations with disability. J Neurol Neurosurg Psychiatry 74: 203-207.
11. Lin X, Tench CR, Morgan PS, Niepel G, Constantinescu CS (2005) 'Importance sampling' in MS: use of diffusion tensor tractography to quantify pathology related to specific impairment. J Neurol Sci 237: 13-19.
12. (2004) Quantitative MRI of the brain: measuring changes caused by disease. John Wiley and Sons Ltd.
13. Ashburner J, Friston KJ (2000) Voxel-based morphometry--the methods. Neuroimage 11: 805-821.
14. Castriota-Scanderbeg A, Sabatini U, Fasano F, Floris R, Fraracci L, Mario MD, Nocentini U, Caltagirone C (2002) Diffusion of water in large demyelinating lesions: a follow-up study. Neuroradiology 44: 764-767.
15. Tievsky AL, Ptak T, Farkas J (1999) Investigation of apparent diffusion coefficient and diffusion tensor anisotrophy in acute and chronic multiple sclerosis lesions. Am J Neuroradiol 20: 1491-1499.
16. Rocca MA, Cercignani M, Iannucci G, Comi G, Filippi M (2000) Weekly diffusion-weighted imaging of normal-appearing white matter in MS. Neurology 55: 882-884.
17. Werring DJ, Brassat D, Droogan AG, Clark CA, Symms MR, Barker GJ, MacManus DG, Thompson AJ, Miller DH (2000) The pathogenesis of lesions and normal-appearing white matter changes in multiple sclerosis: a serial diffusion MRI study. Brain 123 (Pt 8): 1667-1676.
18. Schmierer K, Altmann DR, Kassim N, Kitzler H, Kerskens CM, Doege CA, Aktas O, Lunemann JD, Miller DH, Zipp F, Villringer A (2004) Progressive change in primary progressive multiple sclerosis normal-appearing white matter: a serial diffusion magnetic resonance imaging study. Mult Scler 10: 182-187.
19. Tedeschi G, Gallo A (2005) Multiple sclerosis patients and immunomodulation therapies: the potential role of new MRI techniques to assess responders versus non-responders. Neurol Sci 26 Suppl 4: s209-s212.
20. Droogan AG, Clark CA, Werring DJ, Barker GJ, McDonald WI, Miller DH (1999) Comparison of multiple sclerosis clinical subgroups using navigated spin echo diffusion-weighted imaging. Magn Reson Imaging 17: 653-661.
21. Werring DJ, Clark CA, Barker GJ, Thompson AJ, Miller DH (1999) Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. Neurology 52: 1626-1632.

22. Filippi M, Iannucci G, Cercignani M, Assunta RM, Pratesi A, Comi G (2000) A quantitative study of water diffusion in multiple sclerosis lesions and normal-appearing white matter using echo-planar imaging. Arch Neurol 57: 1017-1021.
23. Filippi M, Cercignani M, Inglese M, Horsfield MA, Comi G (2001) Diffusion tensor magnetic resonance imaging in multiple sclerosis. Neurology 56: 304-311.
24. van Walderveen MA, Kamphorst W, Scheltens P, van Waesberghe JH, Ravid R, Valk J, Polman CH, Barkhof F (1998) Histopathologic correlate of hypointense lesions on T1-weighted spin-echo MRI in multiple sclerosis. Neurology 50: 1282-1288.
25. Bammer R, Augustin M, Strasser-Fuchs S, Seifert T, Kapeller P, Stollberger R, Ebner F, Hartung HP, Fazekas F (2000) Magnetic resonance diffusion tensor imaging for characterizing diffuse and focal white matter abnormalities in multiple sclerosis. Magn Reson Med 44: 583-591.
26. Cercignani M, Bozzali M, Iannucci G, Comi G, Filippi M (2001) Magnetisation transfer ratio and mean diffusivity of normal appearing white and grey matter from patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 70: 311-317.
27. Ciccarelli O, Werring DJ, Wheeler-Kingshott CA, Barker GJ, Parker GJ, Thompson AJ, Miller DH (2001) Investigation of MS normal-appearing brain using diffusion tensor MRI with clinical correlations. Neurology 56: 926-933.
28. Cercignani M, Inglese M, Pagani E, Comi G, Filippi M (2001) Mean diffusivity and fractional anisotropy histograms of patients with multiple sclerosis. Am J Neuroradiol 22: 952-958.
29. Bozzali M, Cercignani M, Sormani MP, Comi G, Filippi M (2002) Quantification of brain gray matter damage in different MS phenotypes by use of diffusion tensor MR imaging. Am J Neuroradiol 23: 985-988.
30. Rovaris M, Iannucci G, Falautano M, Possa F, Martinelli V, Comi G, Filippi M (2002) Cognitive dysfunction in patients with mildly disabling relapsing-remitting multiple sclerosis: an exploratory study with diffusion tensor MR imaging. J Neurol Sci 195: 103-109.
31. Filippi M, Bozzali M, Comi G (2001) Magnetization transfer and diffusion tensor MR imaging of basal ganglia from patients with multiple sclerosis. J Neurol Sci 183: 69-72.
32. Valsasina P, Rocca MA, Agosta F, Benedetti B, Horsfield MA, Gallo A, Rovaris M, Comi G, Filippi M (2005) Mean diffusivity and fractional anisotropy histogram analysis of the cervical cord in MS patients. Neuroimage 26: 822-828.
33. Agosta F, Benedetti B, Rocca MA, Valsasina P, Rovaris M, Comi G, Filippi M (2005) Quantification of cervical cord pathology in primary progressive MS using diffusion tensor MRI. Neurology 64: 631-635.
34. Hickman SJ, Wheeler-Kingshott CA, Jones SJ, Miszkiel KA, Barker GJ, Plant GT, Miller DH (2005) Optic nerve diffusion measurement from diffusion-weighted imaging in optic neuritis. AJNR Am J Neuroradiol 26: 951-956.
35. Trip SA, Wheeler-Kingshott C, Jones SJ, Li WY, Barker GJ, Thompson AJ, Plant GT, Miller DH (2005) Optic nerve diffusion tensor imaging in optic neuritis. Neuroimage.
36. Basser PJ, Pajevic S (2000) Statistical artifacts in diffusion tensor MRI (DT-MRI) caused by background noise. Magn Reson Med 44: 41-50.
37. Lori NF, Akbudak E, Shimony JS, Cull TS, Snyder AZ, Guillory RK, Conturo TE (2002) Diffusion tensor fiber tracking of human brain connectivity: aquisition methods, reliability analysis and biological results. NMR Biomed 15: 494-515.
38. Lazar M, Alexander AL (2003) An error analysis of white matter tractography methods: synthetic diffusion tensor field simulations. Neuroimage 20: 1140-1153.